REMARKS

Status of the Claims

Pending claims

Claims 1 to 14 and 17 to 39 are pending.

Claims amended and added in the instant amendment

In the present response, claims 1 to 13 and 17 to 37 are amended, and new claims 40 to 57 are added. Accordingly, after entry of the instant amendment, claims 1 to 14 and 17 to 57 will be pending and under examination.

Outstanding Rejections

Claims 1 to 3, 13, 14, 17 to 24 and 35 to 39 are rejected under 35 U.S.C. §112, first and second paragraphs. Applicants respectfully traverse all outstanding objections to the specification and rejection of the claims.

Claims 4 to 12 Allowable

Applicants thank the Examiner for finding claims 4 to 12 allowable if re-written in independent form.

Support for the Claim Amendments

The specification sets forth an extensive description of the invention in the new and amended claims. Support for claims directed to methods for making a polypeptide using a nucleic acid of the invention can be found, *inter alia*, on pages 15 to 18 of the specification. Support for claims directed to sequences complementary or identical to that of a gene or a portion of a gene sequence of the invention can be found, inter alia, in the paragraph spanning pages 11 and 12 of the specification. Support for claims directed to diagnostic probes or PCR primers comprising sequences of the invention can be found, inter alia, on page 12, last paragraph. Support for claims directed to nucleic acids of the invention of various lengths can be found, inter alia, on page 8, second full paragraph, on page 12, last paragraph, and the first paragraph on page 13.

Information Disclosure Statement

Applicants thank the Examiner for expressly considering (and initialing) the Information Disclosure Statements (IDSs) and Forms PTO-1449, including the first IDS submitted July 31, 1998, and the supplemental IDSs and Forms PTO-1449 filed March 17, 2000, August 23, 2000, and July 11, 2003.

Issues under 35 U.S.C. §112, first paragraph

Written Description

Aminotransferase activity

Claims 1 to 3, 13, 14, 17 to 24 and 35 to 39 are rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors at the time the application was filed had possession of the claimed invention.

The Patent Office alleges that a DNA encoding an aminotransferase of an unknown specificity towards donor and acceptor of the amino group and having an amino acid sequence which is at least 70% identical to the exemplary sequence of the invention lack sufficient written description.

The instant amendment addresses this issue. After entry of the instant amendment, claim 1 is directed to isolated or recombinant polynucleotides encoding polypeptides having a genus of aminotransferase activities comprising alternative species of aminotransferase activities.

Hybridization conditions

Claims 17 to 24 and 35, are drawn to probes defined by, inter alia, hybridization under specific conditions (after entry of the instant amendment, see claims 36 to 39 and 49 to 57, directed to probes and primers).

The office action notes that the hybridization conditions may be at very low stringency. This instant amendment addresses this issue. After entry of the instant amendment, hybridization conditions comprise washing under stringent conditions.

It is alleged, inter alia, that the specification does not contain any disclosure of the

structure and function of all nucleic acids which will hybridize to a region or entire polynucleotide encoding any one of the exemplary nucleic acids under the claimed hybridization conditions, and that many structurally and functionally unrelated nucleic acids are encompassed by the scope of the claims. Applicants respectfully submit that the claimed invention is sufficiently described in the specification such that one of ordinary skill in the art would be able to ascertain the scope of the claims with reasonable clarity and recognize that Applicants' were in possession of the claimed invention at the time of filing. Applicants respectfully aver that a single species of a genus can be sufficient to put one of skill on the art in possession of all species with a claimed genus.

Applicants respectfully submit that only structurally and functionally related nucleic acids are encompassed by the scope of the claims. The nucleic acids of the claimed invention are described by structure (the exemplary sequences), a physico-chemical property (percent sequence identity and/or hybridization conditions) and function (aminotransferase activity). All nucleic acids of the claimed genus must encode an enzyme having at least about 70% sequence identity to an exemplary aminotransferase. Applicants respectfully submit that describing a genus of polynucleotides in terms of physico-chemical properties (e.g., sequence identity or hybridization conditions) and function (e.g., encoding polypeptides having transaminase activity) satisfies the written description requirement of section 112, first paragraph.

The Patent Office also alleged that a single species of a genus is insufficient to put one of skill on the art in possession of all species with a claimed genus. Applicants respectfully note that they have set forth several representative species of a genus of transaminases of the invention, including enzymes having a sequence as set forth in SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28, SEQ ID NO:29, SEQ ID NO:30, SEQ ID NO:31, or SEQ ID NO:32.

However, Applicants respectfully aver that even a single species of the instant invention is sufficient to put one of skill on the art in possession of the claimed genus. There is no bright line rule that a single species of a genus is insufficient to put one of skill on the art in possession of all species with a claimed genus. Applicants respectfully refer to the USPTO guidelines concerning compliance with the written description requirement of U.S.C. §112, first

paragraph. In example 14 of the guidelines (a copy of which is attached as Exhibit A), a claim reciting variants claimed by sequence identity to a sequence is sought (specifically, "A protein having SEQ ID NO:3 and variants thereof that are at least 95% identical to SEQ ID NO:3 and catalyze the reaction of A → B). In the example, the specification is described as providing SEQ ID NO:3 and a function for the protein. The specification contemplates, but does not exemplify variants of SEQ ID NO:3 that can have substitutions, deletions, insertions and additions. Procedures for making proteins with substitutions, deletions, insertions, and additions are routine in the art and an assay is described which will identify other proteins having the claimed catalytic activity. The analysis of example 14 states that procedures for making variants (which have 95% sequence identity) are conventional in the art. The Guidelines conclusion states that the disclosure meets the requirements of 35 U.S.C. §112, first paragraph, as providing adequate written description for the claimed invention.

Analogously, the genus of nucleic acids of the claimed invention is described by structure (the exemplary nucleic acids or polypeptide sequences), a physico-chemical property (percent sequence identity or stringent hybridization conditions) and function (having a transaminase activity). All nucleic acids of the genus used in the claimed methods must have at least 70% or more sequence identity to an exemplary sequence of the invention. The USPTO guidelines recognize that written description is met for a genus of polypeptides described by structure, a physico-chemical property (e.g., a % sequence identity) and a defined function, the genus of claimed polypeptides also meet the written description requirements of section 112.

The genus of nucleic acids of the claimed invention also fully comply with the requirements for written description of a genus of nucleic acids as set forth in University of California v. Eli Lilly & Co., 43 USPQ2d 1398 (Fed. Cir. 1997). In Lilly, the Court stated that, "[a] description of a genus of cDNA may be achieved by means of a recitation of a representative number of cDNAs....*or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus.*" (emphasis added) Lilly, 43USPQ2d at 1406.

As noted above, the instant claims clearly set forth specific structural and physical characteristics of the claimed transaminase-encoding nucleic acids. The claimed genus of polypeptides all must have a transaminase activity and a specific physical characteristic, e.g., a %

sequence identity to the exemplary nucleic acid. Therefore, the genus of nucleic acids used in the claimed methods is defined via shared physical and structural properties in terms that "convey with reasonable clarity to those skilled in the art that Applicant, as of filing date sought, was in possession of invention." (Vas-Cath Inc. V. Mahukar, 19 USPQ2d 1111, (Fed Cir. 1991)).

More recently, the Federal Circuit stated

Similarly, in this court's most recent pronouncement, it noted:

> More recently, in Enzo Biochem, we clarified that Eli Lilly did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure.

Amgen, 314 F.3d at 1332 [Amgen Inc. v. Hoechst Marion Roussel Inc., 314 F.3d 1313, 1330, 65 USPQ2d 1385, 1397 (Fed. Cir. 2003)].

Moba, B.V. v. Diamond Automation, Inc., 2003 U.S. App. LEXIS 6285; Fed. Cir. 01-1063, -1083, April 1, 2003.

Analogously, the function of the transaminases encoded by the nucleic acids of the invention is sufficiently correlated to a particular, known structure (the exemplary sequences) and a physical (physico-chemical) property (percent sequence identity or specific hybridization conditions). Accordingly, the sequences used in the claimed methods are defined via shared physical and structural properties in terms that convey with reasonable clarity to those skilled in the art that Applicants, as of the filing date and at the time of the invention, were in possession of the claimed invention.

Applicants also respectfully refer to recently issued claims directed to genuses of polynucleotides based on sequence identity (and stringent hybridization) to an exemplary nucleic acid, see, e.g., recently issued claims directed to, e.g., 72.5% sequence identity, as in USPN 6,593,514; 75% sequence identity, as in USPN 6,586,215; 80% sequence identity, as in USPN 6,596,926; 85% sequence identity, as in USPN 6,590,141 and USPN 6,586,179; 86% sequence identity, as in USPN 6,583,337; 90% sequence identity (and "stringent hybridization"), as in USPN 6,541,684 (see Exhibit B).

Accordingly, Applicants respectfully submit that the pending claims meet the written description requirement under 35 U.S.C. §112, first paragraph. In light of the above

remarks, Applicants respectfully submit that amended claims are fully enabled by and described in the specification to overcome the rejection based upon 35 U.S.C. §112, first paragraph.

Enablement

Aminotransferase activity

Claims 1 to 3, 13, 14, 17 to 24 and 35 to 39 are rejected under 35 U.S.C. §112, first paragraph, as allegedly not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention.

The Patent Office states that the specification is enabling for a polynucleotide encoding a specific aminotransferase having one of the exemplary amino acid sequences, and fragments thereof.

However, it is alleged that the specification does not provide reasonable enablement for a polynucleotide encoding a transaminase or aminotransferase of an undefined specificity.

Applicants respectfully submit that the instant amendment addresses this issue. After entry of the instant amendment, claim 1 is directed to isolated or recombinant polynucleotides encoding polypeptides having a genus of aminotransferase activities comprising alternative species of aminotransferase activities.

Modification and fragments

The Patent Office alleges that claims 25 to 32 and 34, drawn to polynucleotides defined by percent sequence identity to exemplary sequences of the invention, and claims 17 to 24 and 35 to 39, drawn to polynucleotides defined by their ability to hybridize to exemplary sequences of the invention under defined conditions, are not enabled by the specification because, inter alia, it would require undue experimentation for one skilled in the art to arrive at the genus of claimed nucleic acids. In particular, it is alleged that it is not routine experimentation to screen for multiple substitutions or multiple modifications with a reasonable expectation of success, and that it would have required some knowledge or guidance as to where modifications can be made to create variants and test them for activity.

Applicants respectfully maintain that the specification enabled the skilled artisan at the time of the invention to identify, and make and use, the claims genus of transaminase-

encoding nucleic acids. As declared by Dr. David Weiner (see attached Rule 132 declaration), the state of the art at the time of the invention and the level of skill of the person of ordinary skill in the art, e.g., screening enzymes, and nucleic acids encoding enzymes, for transaminase activity, was very high. As declared by Dr. Weiner, using the teaching of the specification, one skilled in the art could have selected routine methods known in the art at the time of the invention to express variants of nucleic acids encoding the exemplary enzymes of the invention and screen them for expression of polypeptides having transaminase activity. Dr. Weiner declares that one skilled in the art could have used routine protocols known in the art at the time of the invention, including those described in the instant specification, to screen for nucleic acids encoding polypeptides having 70% sequence identity to an exemplary sequence of the invention, or active fragments thereof, for transaminase activity. Dr. Weiner declares that one skilled in the art could have used routine protocols known in the art at the time of the invention, including those described in the instant specification, to screen for nucleic acids capable of hybridizing under the specific conditions set forth in the specifictation to exemplary sequences of the invention, or active fragments thereof, for transaminase activity.

As declared by Dr. Weiner, while the numbers of samples needed to be screened may have been high, the screening procedures were routine and successful results (i.e., finding variant nucleic acids encoding transaminase) predictable. Furthermore, Dr. Weiner declares that it would not have required any knowledge or guidance as to where modifications needed to be made to create variants having transaminase activity. Dr. Weiner declares that it would not have required any knowledge or guidance as to which are the specific structural elements, e.g., amino acid residues, that correlate with transaminase activity to create variants of the exemplary nucleic acids and test them for the expression of polypeptides having transaminase activity. Accordingly, it would not have taken undue experimentation to make and use the claimed invention, including identification of a genus of nucleic acids encoding transaminases.

Whether large numbers of compositions (e.g., enzymes, antibodies, nucleic acids, and the like) must be screened to determine if one is within the scope of the claimed invention is irrelevant to an enablement inquiry. Enablement is not precluded by the necessity to screen large numbers of compositions, as long as that screening is "routine," i.e., not "undue," to use the words of the Federal Circuit. The Federal Circuit in In re Wands directed that the focus of the

enablement inquiry should be whether the experimentation needed to practice the invention is or is not "undue" experimentation. The court set forth specific factors to be considered.

One of these factors is "the quantity of experimentation necessary." Guidance as to how much experimentation may be needed and still not be "undue" was set forth by the Federal Circuit in, e.g. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). In Hybritech, Inc., a single deposited antibody producing cell line enabled a claim generic to all IgM antibodies directed to a specific antigen. The Federal Circuit noted that the evidence indicated that those skilled in the monoclonal antibody art could, using the state of the art and applicants' written disclosure, produce and screen new hybridomas secreting other monoclonal antibodies falling within the genus without undue experimentation. The court held that applicants' claims need not be limited to the specific, single antibody secreted by the deposited hybridoma cell line (significantly, the genus of antibodies was allowed even though only one antibody specie was disclosed). The court was acknowledging that, because practitioners in that art are prepared to screen large numbers of negatives in order to find a sample that has the desired properties, the screening that would be necessary to make additional antibody species was not "undue experimentation."

Analogously, practitioners of the biological sciences for the instant invention also recognize the need to screen numbers of negatives to find a sample that has the desired properties, e.g., transaminase activity. Furthermore, as declared by Dr. Weiner, the screening procedures used to identify nucleic acids within the scope of the instant invention (e.g., identifying nucleic acids encoding transaminases) were all well known in the art and at the time this application was filed. All were routine protocols for the skilled artisan. Thus, the skilled artisan using Applicants' written disclosure could practice the instant claimed invention without undue experimentation.

Enablement is not precluded by the necessity to screen large numbers of alternative compounds (e.g., nucleic acids or polypeptides), as long as that screening is "routine," i.e., not "undue." As declared by Dr. Weiner, it would have taken only routine protocols to make variants of the exemplary nucleic acids and screen them to identify those that encode polypeptides with transaminase activity. Thus, the specification enabled the skilled artisan at the time of the invention to make and use a broad genus of transaminases of the present invention.

Issues under 35 U.S.C. §112, second paragraph

Claims 1 to 3, 13, 14, 17 to 24 and 35 to 39 stand rejected under 35 U.S.C. §112, second paragraph, for allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The phrase "an enzyme with aminotransferase activity"

The Patent Office alleged claim 1 is indefinite because of the phrase "an enzyme with aminotransferase activity". The instant amendment addresses this issue. After entry of the instant amendment, claim 1 is directed to isolated or recombinant polynucleotides encoding polypeptides having specific aminotransferase activities.

The term "a region"

The Patent Office alleged claim 17 is indefinite because of the term "a region". The instant amendment addresses this issue.

CONCLUSION

In view of the foregoing amendment and remarks, it is believed that the Examiner can properly withdraw the rejection of the pending claims under 35 U.S.C. §112, first and second paragraphs. Applicants believe all claims pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

Applicants believe that no additional fees are necessitated by the present response and amendment. However, in the event any such fees are due, the Commissioner is hereby authorized to charge any such fees to Deposit Account No. 06-1050. Please credit any overpayment to this account.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (858) 678-5070.

Respectfully submitted,

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